HOSPITAL LIBRARY

VOLUME LXXIX

NUMBER 3

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

September, 1946

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

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BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

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This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

NECROSIS AND ULCERATION OF THE INTESTINAL WALL IN SIMPLE INTESTINAL OBSTRUCTION

An Experimental Study

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From the Department of Surgery of the Henry Ford Hospital

INTRODUCTION

The cause of death in simple intestinal obstruction has been the source of extensive and thorough research and hundreds of articles for the past 50 years. From 1900 to 1920 the chief cause of death was thought to be the absorption of a toxin, probably of bacterial origin. During this time little was accomplished in regard to the treatment of this condition and the mortality rate remained high. From 1920 to the present time, research work has been carried on which has revealed the great importance in replacing lost electrolytes (7, 11, 13, 14, 21, 25) and fluid (17, 18) and in relieving distension by intubation (3, 20, 39). This has led to the present widely accepted belief that it is possible to account for all the symptoms and signs and death in simple intestinal obstruction on the basis of loss of water and electrolytes and the mechanical effects of distension. There has been a marked tendency to minimize any possible role that bacteria could play in simple intestinal obstruction.

Best and Taylor, in their "Physiological Basis of Medical Practice," 1944 (6), state that "A bacterial theory in one or the other of its modifications has had its adherents. The "toxin" of the Welch bacillus has been suspected by some, but little support has been given by recent work to the belief that this or any other bacterial "toxin" is responsible for the symptoms (of intestinal obstruction.)" They also state that "It is impossible to consider seriously any bacterial theory of intestinal obstruction for such theories ignore the fact that the symptoms diminish in intensity and the survival time is lengthened the lower in the intestinal tract the obstruction is produced."

It has been known, however, that many textbooks of pathology describe an ulcerative process that is found in cases of simple obstruction. In 1907, while doing experimental work on intestinal obstruc-

tion in dogs, R. D. McClure pointed out that, "Even in simple obstruction of the intestine it is not uncommon to find in the walls of the distended loop, changes which sometimes cause perforation. In several of our experiments autopsy revealed an acute general peritonitis which had resulted from the formation of ragged ulcers above the obstruction in the distended hemorrhagic wall" (22). In autopsy reports of human cases of simple intestinal obstruction it is often observed that the ulceration has become deep enough to cause a perforation with a resulting general peritonitis. For example McKittrick reported autopsy findings on 29 cases of acute small bowel obstruction. 5 of these died of pneumonia. 3 died from miscellaneous causes 21 died as a result of intestinal obstruction. 17 of these or 81% had ulcerations of the intestinal wall with perforation and general peritonitis (24).

Last year a problem was undertaken to re-investigate the role of bacteria in producing death in dogs having isolated obstructed jejunal loops. It was found that large doses of penicillin would markedly delay in all cases and prevent in most cases the ulceration of the intestinal wall that occurs in obstructed isolated loops. (16) The question was then asked, "Does a similar ulcerative process occur in simple intestinal obstruction?" The aim of this problem is to establish:

(1) How often does this process of hemorrhage, necrosis and ulceration occur in simple intestinal obstruction in dogs?

(2) How extensive is this process?

(3) At what levels of obstruction does this process occur?

(4) What is the cause of this process?

EXPERIMENTAL METHODS

Simple intestinal obstruction was artificially produced in 10 dogs at the level of the ligament of Treitz or 20 cm. below the pylorus, in 10 dogs in the mid ileum or 100 cm. distal to the ligament of Treitz, and in 10 dogs in the terminal ileum or about 5 cm. proximal to the ileocecal junction (Fig. 1). The obstruction was produced by dividing the intestine between Stone clamps and inverting both ends of the cut intestine by the Parker-Kerr procedure. A single silk suture was used. The operative time averaged about twenty minutes. Only healthy dogs weighing between 20 and 35 lbs. were used. All dogs in

FIG. 1. Alimentary canal of normal dog. Ten dogs were obstructed at each of the three arrows 1, 2, and 3, i.e. Lig. of Treitz, mid ileum, and ileocecal junction.

this series were operated on under intravenous nembutal anesthesia. There were two anesthetic deaths. Picrotoxin was used when neces-

sary for the relief of respiratory depression. All dogs were weighed at operation and at autopsy. Fluid intake (water) and output (vomitus and urine) data was recorded daily on each dog. Four dogs developed postoperative pneumonia. These dogs were not included in the series. One dog with high obstruction and another dog with mid obstruction developed a leak at the proximal turned in stump and both died with general peritonitis. These two dogs were not included. Food was withheld for twenty-four hours before the operation and for the duration of life following operation. All dogs were allowed to drink water *ad libitum* to 1000 cc. a day following operation but received no electrolytes or food. The intestine was cultured at the site of obstruction at time of operation. All dogs had an autopsy performed as soon as possible after death. At autopsy the heart blood and peritoneal and intraluminal cultures just above the site of obstruction were taken. The intestine was photographed unopened and opened. The most important structures were then placed in 10% formalin. Microscopic sections of the most important lesions were made and hematoxylin and eosin and bacterial stains were done on sections of the intestine. Representative portions of the sections were then microphotographed.

RESULTS

The results of this series of experiments show that damage to the intestinal wall occurred in none of dogs with high intestinal obstruction, 70% of dogs with mid ileal obstruction, and 80% of dogs with terminal ileal obstruction (Table 2). There was an average area of 0 sq. cm. of hemorrhage and necrosis in high obstruction (Fig. 4), 9.6 sq. cm. in mid ileal obstruction (Fig 6), and 18.3 sq. cm. in low ileal obstruction (Fig 8). Actual ulceration occurred in no case of high obstruction, 30% of mid-ileal obstructions and 30% of low ileal obstructions. Four of the six cases that revealed ulceration also showed a local peritonitis on the serosal surface microscopically (Fig. 13, 14). There were no cases of gross perforation of the intestine followed by general peritonitis. Distension was found to be greater and to occur sooner the lower the obstruction. Kinking of the bowel with the resulting formation of partially or completely obstructed isolated loops with an intact blood supply occured in no case of high obstruction but in most cases of mid ileal and low ileal obstruction. All dogs in this

TABLE 1

Individual Results

	DOG	WEIGHT LOSS	SURVIVAL TIME	HEM. NECR. AND ULCER.	PANCREATIC ACTIVITY	DEGREE OF DISTENSION	SEMI-COMATOSE CONDITION	FLUID INTAKE	FLUID OUTPUT	PERITONITIS	PERFORATION OF INTESTINE	ATROPHY OF PANCREAS	KINKING OF INTESTINE
High													
		lbs.	*days*			*cm.*		*cc.*	*cc.*				
1	59	4½	11	0		2½	0	4560	3770	0	0	2/3	0
2	101	4½	10	0	1/400	2¾	0	4620	5555	0	0	1/2	0
3	107	6½	5	0	1/400	2¼	0	6600	6605	0	0	1/2	0
4	117	5	13	0	1/400	3	0	7350	6350	0	0	2/3	0
5	118	4½	8	0	1/400	2¼	0	3590	2725	0	0	1/2	0
6	119	3½	6	0	1/50	2	0	2340	2540	0	0	1/2	0
7	121	4½	9	0	1/400	2	0	3641	3485	0	0	2/3	0
8	123	4½	8	0	1/400	3	0	2195	2205	0	0	1/2	0
9	124	5½	14	0	1/400	2¼	0	4675	4075	0	0	1/2	0
10	130	6	6	0	1/400	2	0	6250	6000	0	0	1/3	0
Mid													
				sq. cm.									
1	98	3	4	0	1/6	2½	0	4000	3190	0	0	1/3	2+
2	108	2½	4	6	1/6	2¼	0	2570	2580	0	0	1/2	2+
3	99	5	5	5	1/6	3	0	4000	3030	0	0	1/2	2+
4	109	3½	6	0	1/100	3¾	0	4080	3400	0	0	1/2	2+
5	126	3½	4	0	1/100	2	0	2450	2910	0	0	1/2	0
6	127	8½	4	20	1/200	3	0	4000	5165	0	0	1/2	3+
7	129	2½	7	10	1/6	3	0	2915	1980	0	0	1/2	3+
8	131	8½	9	30	1/6	4	+	5470	4945	local	Micro.	2/3	4+
9	138	4½	4	10	0	2¾	+	3750	3030	0	0	1/3	3+
10	142	7½	8	15	1/200	3¾	0	5450	5035	0	0	1/2	3+
Low													
1	96	7	7	50	1/2	4¾	+	7130	6275	local	Micro.	1/2	4+
2	97	4	7	35	1/2	3½	+	5250	4580	local	Micro.	1/2	4+
3	104	3	4	15	1/100	3¼	0	2985	1930	0	0	1/2	3+
4	105	3	4	7	1/100	2¾	0	2310	2430	0	0	1/2	2+
5	111	5	5	6	1/25	3¾	0	6000	4670	0	0	1/2	2+
6	112	3½	8	20	1/3	3¾	+	4290	3120	0	0	2/3	4+
7	113	15	26	0	0	6–8	0	9405	8640	0	0	2/3	4+
8	114	4½	6	15	1/3	3½	0	3030	2930	0	0	1/2	2+
9	115	3	3	2	1/50	3	0	2320	2070	0	0	1/3	2+
10	145	4	7	30	1/50	3½	+	5020	4145	local	Micro.	1/2	3+

series became very weak before death but only dogs with ulceration of the bowel were comatose (i.e. could not be aroused) before death. It is very interesting to note that the results of this series of experiments indicates that when water is given *ad libitum* to dogs with simple obstruction the well established concept that the higher the obstruction

TABLE 2

Summary of Results

SUMMARY OF RESULTS		HIGH	MID.	LOW
Average total area of hemorrhage and necrosis of intestine at death		0	9.6 sq. cm.	18.3 sq. cm.
Percentage of cases showing hemorrhage and necrosis of intestine		0	70%	80%
Percentage of cases showing no hemorrhage or necrosis of intestine		100%	30%	20%
Percentage of cases showing actual ulceration		0	30%	30%
Average degree of distension as measured by diameter of bowel		2.25 cm.	3.00 cm.	3.97 cm.
Degree of kinking of intestine forming isolated loops	0	100%	10%	0
	1+	0	0	0
	2+	0	40%	40%
	3+	0	40%	20%
	4+	0	10%	40%
Percentage of cases showing comatose period		0	20%	40%
Average survival time		9 days	5.5 days	7.7 days
Average pancreatic activity of intestinal content at death		235	12	5
Degree of pancreatic atrophy		$\frac{1}{2}$ to $\frac{2}{3}$	$\frac{1}{2}$	$\frac{1}{2}$
Average weight loss		4.9 lbs.	5 lbs.	5 lbs.
Percentage of positive blood cultures at death		10%	20%	30%
Percentage of negative blood cultures at death		90%	80%	70%
Percentage of positive peritoneal cultures at death		40%	20%	70%
Percentage of negative peritoneal cultures at death		60%	80%	30%

the less the survival time (26, 27), no longer holds true. Instead it is then found that dogs with high obstruction live longer than dogs with low intestinal obstruction (Fig 2).

The average survival time of dogs with high intestinal obstruction was 9 days, mid ileal obstruction 5.5 days and low ileal 7.7 days. Something should be said about dog 113 who outlived by over three times the average survival time of the other dogs with terminal

obstruction. This dog drank water in sips over a long period of time throughout the day and was never known to vomit during the entire 26 days of survival. The distension occured much more slowly than

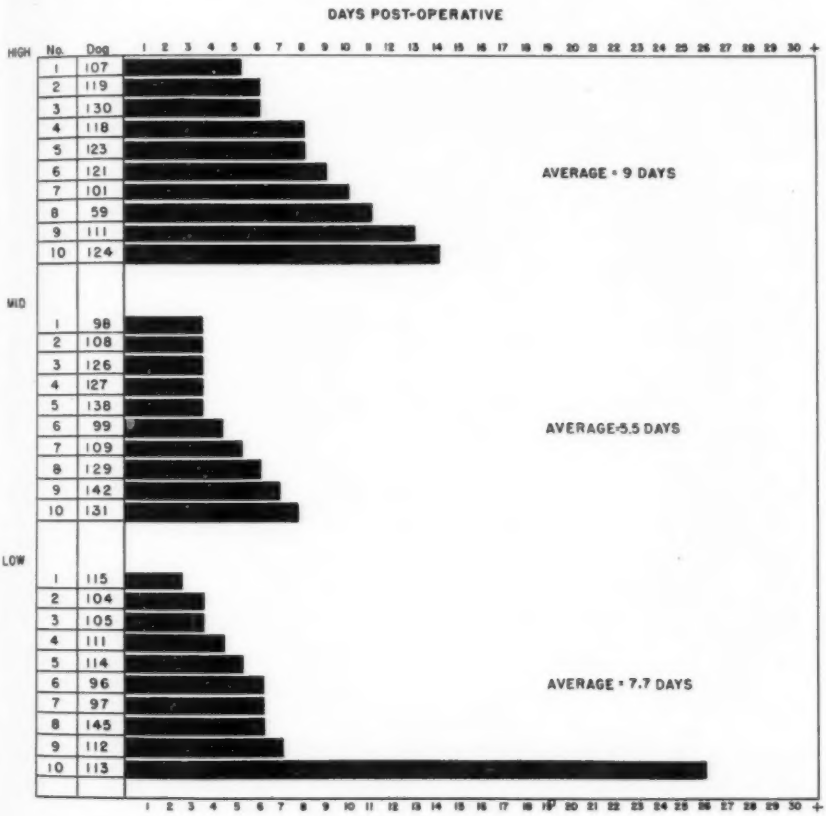

FIG. 2. SURVIVAL TIME

in the other dogs and was not marked until about the 18th postoperative day. At autopsy although enormous distension was present, no evidence of hemorrhage, necrosis or ulceration was found along the entire intestinal tract.

The average pancreatic activity of the intestinal content above

site of obstruction at autopsy was tested by the Anderson-Early procedure (4) and was found to be of a standard potency in a dilution of $\frac{1}{2\frac{1}{3}5}$ in high obstruction, $\frac{1}{1\frac{1}{2}}$ in mid ileal obstruction and $\frac{1}{5}$ in low ileal

FIG. 3. Dog 59—High obstruction—lived 11 days. Intestine shows very little distension. Pancreas shows marked atrophy.

obstruction. This indicates that activated pancreatic juice is not an important cause of necrosis and ulceration of the intestinal wall in simple intestinal obstruction as the lower the obstruction the greater the area and incidence of necrosis and ulceration and yet the less is the

pancreatic activity of the intestinal content found at that level at autopsy. An incidental autopsy finding was that the pancreas was found to have undergone an average atrophy of two-thirds in high

FIG. 4. Dog 59—High obstruction. Intestine opened along mesenteric border. Mucosa normal except bile stained.

obstruction (Fig. 3), one-half in mid obstruction and one-half in low obstruction. The average weight loss was about the same at all levels of obstruction: 4.9 lbs. for high obstruction, 5 lbs. for mid ileal obstruc-

FIGS. 5–6

tion and 5 lbs. for low ileal obstruction. Although only one silk suture was used to turn in the intestine it is interesting to note that even in the presence of a complete intestinal obstruction only two dogs out of 38 had a "blow out" of the turned in intestinal stump. The percentage of positive blood cultures at autopsy was 10% for high obstruction, 20% for mid ileal obstruction and 30% for low ileal obstruction. The percentage of positive peritoneal cultures was 40% for high obstruction, 20% for mid ileal obstruction and 70% for low ileal obstruction. It should be pointed out that these cultures were taken at autopsy and would be much more dependable if they had been taken just before death. However, it is interesting to note that these results check with the observation that there is a larger area of necrosis and ulceration the lower the site of obstruction, such increased bowel wall damage would provide a more accessible portal of entry to the peritoneum and the blood stream.

DISCUSSION

Three of the original questions proposed have now been answered.

1. How often does this process of hemorrhage, necrosis and ulceration occur in simple intestinal obstruction in dogs?

2. How extensive is this process?

3. At what levels of obstruction does this process occur?

The question remains. What is the cause of this process?

1. Is distension alone responsible?

a. Previous experiments which show that distension is responsible were carried out without regard to the presence of bacteria in the intestinal lumen.

b. In a previous series of experiments we were able to show that this process of necrosis and ulceration occurring in isolated loops could be significantly delayed in all cases and prevented in most cases when

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FIG. 5. Dog 131—Mid ileal obstruction—lived 9 days. Intestine above obstruction markedly distended and kinked on itself forming multiple isolated loops. Intestine below obstruction atrophied.

FIG. 6. Dog 131—Mid ileal obstruction. Intestine opened along mesenteric border showing hemorrhage, necrosis and ulceration along the antimesenteric border.

FIGS. 7–8

enormous doses of penicillin were given prophylactically. Even though these penicillin treated loops became distended, and developed petechial hemorrhages in the mucosa, the loop content remained odorless and sterile, the dogs did not die and when the loop was removed at operation for examination there was no necrosis or ulceration present (16).

c. It is conceivable that a prolonged distension of the bowel would result in an ischemic necrosis of the intestine if there were no bacteria present but with the enormous numbers of many different kinds of bacteria normally present in the bowel, distension does not have the opportunity to act by itself. The bacteria present infect the tissue damaged by distension and acute inflammatory reaction with ulceration and bacterial necrosis occurs. Bacteria and their products may then gain access to the peritoneum and to the blood stream even before a gross perforation of the intestine occurs.

2. Is activated pancreatic secretion in the presence of distension responsible?

a. Another series of experiments were carried out to determine this. The results will be reported in a later article. However, additional evidence was found in this experiment that pancreatic juice is not responsible. It was found that the lower the obstruction the greater the incidence and area of hemorrhage, necrosis and ulceration, yet it was also found that the lower the obstruction the less was the pancreatic activity of the intraluminal content found above the site of obstruction at autopsy (Table 2).

3. Are bacteria in the presence of distension responsible?

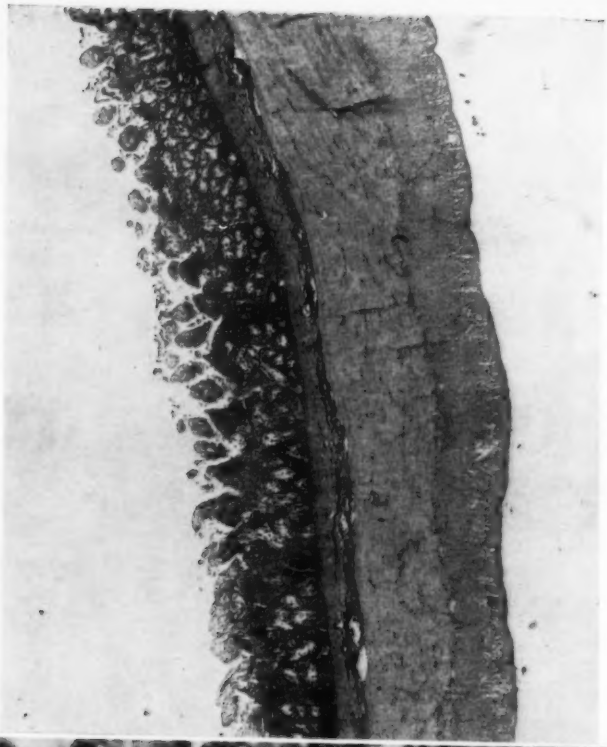
a. The lower the obstruction the greater is the incidence and area of hemorrage and necrosis and ulceration, and as Best and Taylor inferred in one of the foregoing quotations, bacteria are found in greater numbers in the lower intestinal tract.

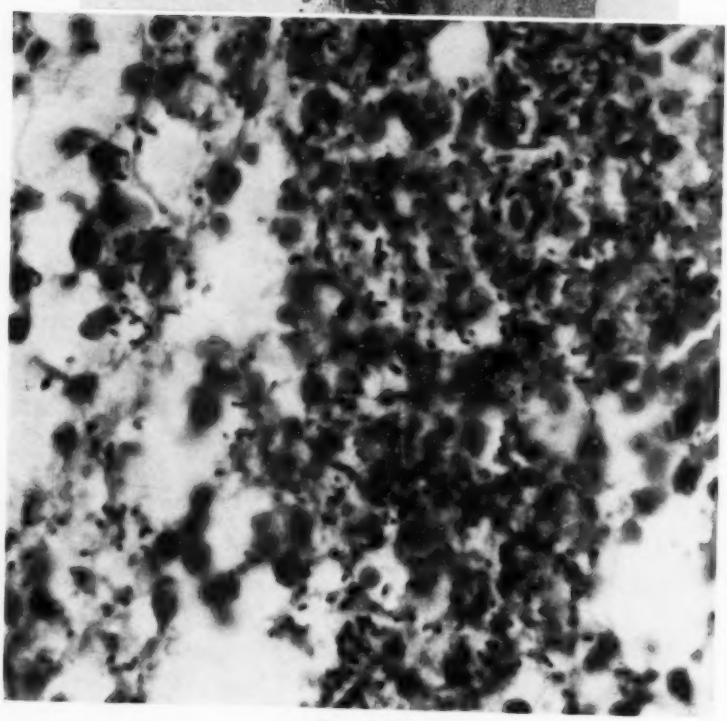
b. The great prophylactic effect of penicillin on this process in

---

FIG. 7. Dog 96—Low ileal obstruction—lived 7 days. Intestine above obstruction is markedly distended and kinked on itself to form multiple isolated loops. Areas of local peritonitis can be seen along the antimesenteric border.

FIG. 8. Dog 96—Terminal ileal obstruction. Intestine opened along mesenteric border revealing a large ragged ulceration along the antimesenteric border.





FIGS. 9–10

isolated loop studies has been mentioned. Edgar H. Poth has in general obtained similar results using sulfasuxidine. (32)

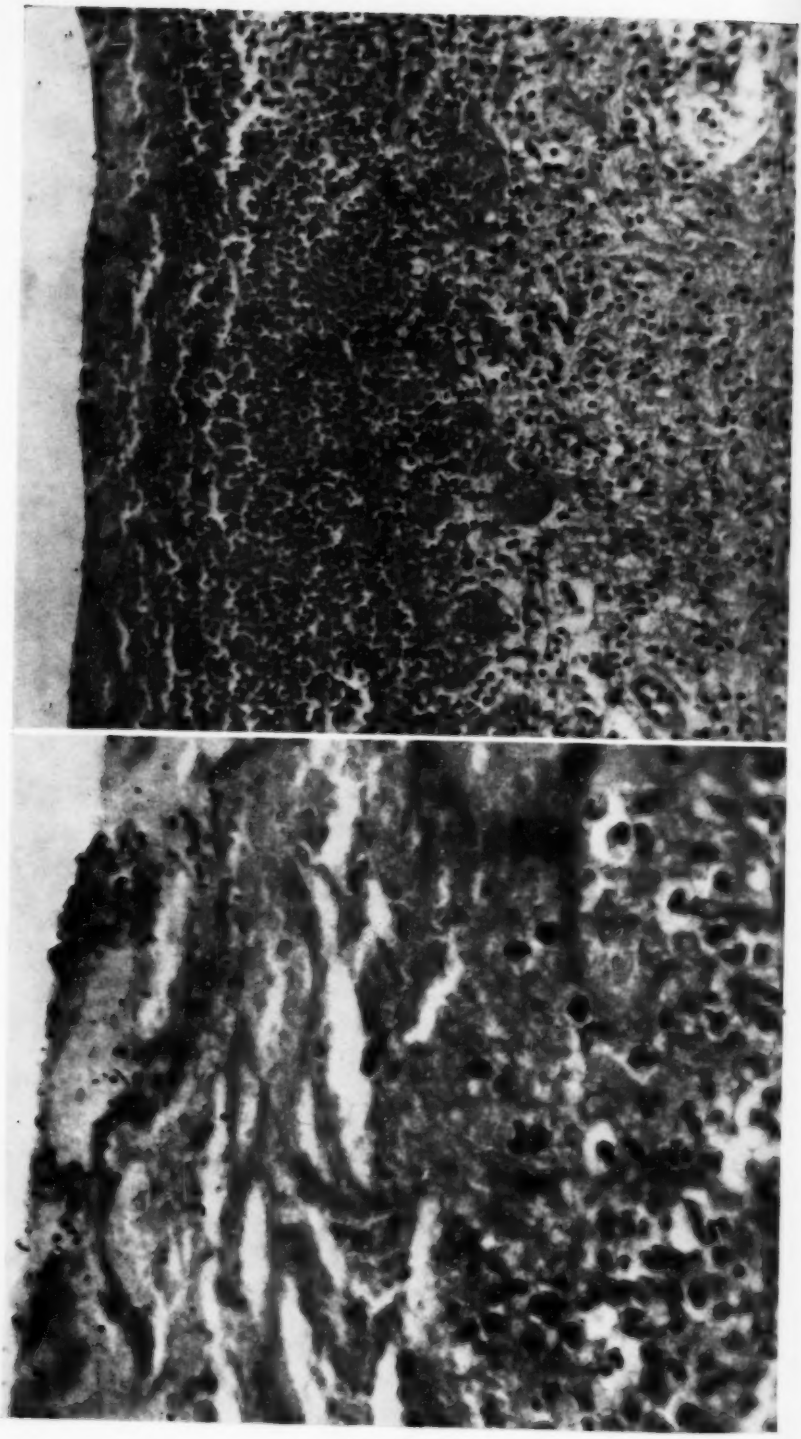
c. Sections of these lesions were taken in the various stages of their development revealing microscopically that congestion of the vessels along the antimesenteric border with the subsequent development of small petechial hemorrhages in the mucosa was the first noticeable change. As the hemorrhagic areas become larger the presence of colonies of bacteria appear associated with tissue necrosis and large numbers of polymorphonuclear neutrophilic leukocytes (Fig. 9, 10). The bacterial colonies increase in number, the polymorphonuclear neutrophilic leukocytes increase in number, the ulceration becomes deeper (Fig. 11, 12) and if unchecked results in bowel perforation and peritonitis (Fig. 13, 14). The normal bacterial flora of the small intestine consist essentially of saprophytes *E. coli*, *Cl. welchi*, *Strep. fecalis*, *proteus*, *aerogenes*, anerobic Strep. While these saprophytic bacteria are not ordinarly classed as pathogens, they have the capacity to become pathogenic under certain conditions i.e. *E. coli* can infect and ulcerate the walls of the urinary tract in the presence of distension due to urinary obstruction; *Cl. welchi* can become a virulent pathogen if the skin is damaged providing a portal of entry to the underlying tissues. Thus saprophytes under these conditions may not only produce tissue necrosis and inflammatory changes but may produce toxins that have profound systemic effects. Saprophytic bacteria will not ordinarily infect the normal intestinal wall until the tissue on the antimesenteric border is first damaged mechanically by distension. Thus, it is of great importance to stress that this process of ulceration will not occur if distension is successfully prevented or relieved.

The importance of the process of kinking in simple intestinal obstruction should be pointed out. A horizontal tube with an open lumen will have the same pressure at all levels unless it is distended in

---

FIG. 9. Dog 104—Stage 2,60 × H & E stain. Antimesenteric border of intestine showing hemorrhage into mucosa with edema and clubbing of the villa. The submucosal vessels are congested. Muscular layers and serosa are normal.

FIG. 10. Dog 104—Stage 2,400 × Bacterial stain. Section from base of mucosa along antimesenteric border. A colony of bacteria is shown. PMN and RBC are present.



FIGS. 11–12

such a small space that it is forced to kink on itself. The duodenum is fixed and there is no chance for kinking. Any increased intra-luminal pressure that develops is relieved by vomiting and thus a high intra-luminal pressure cannot be present for long (Fig. 3) in the duodenum. There is however a greater chance for more kinding to take place the lower the site of obstruction (Fig. 5, 7). This kinking eventually becomes marked enough so that actual isolated loops are produced with an intact blood supply. The ulceration takes place on the antimesenteric border in the center of these loops and not in the angulated area (Fig. 6, 8). The process is thus similar but not as extensive as the process found to occur in experimental isolated intestinal loops.

Dogs with simple high obstruction given water *ad libitum* to drink vomited more than dogs with low simple obstruction. However, the total fluid output up until death was about the same (Table 1). The dogs with low obstruction vomited less but urinated more. If water, electrolytes and food are withheld from dogs with high simple obstruction they will die within two to five days. Our series of dogs with high simple obstruction given water *ad libitum* to drink lived an average of nine days. This indicates that in the early stages of simple high intestinal obstruction water loss thru vomiting is a very important cause of death. However, loss of electrolytes also plays an important role. If dogs with simple high intestinal obstruction are given electrolytes in addition to water they may be kept living twenty-one to twenty-six days or until they die from starvation (17). Distension followed by necrosis and ulceration of the intestinal wall develops so slowly in high intestinal obstruction that it could only occur if the dog was kept living by replacement of water and electrolytes and in some cases only if the starvation was also combated by intravenous protein therapy.

It appears to be naive to say that there is any single cause of death in

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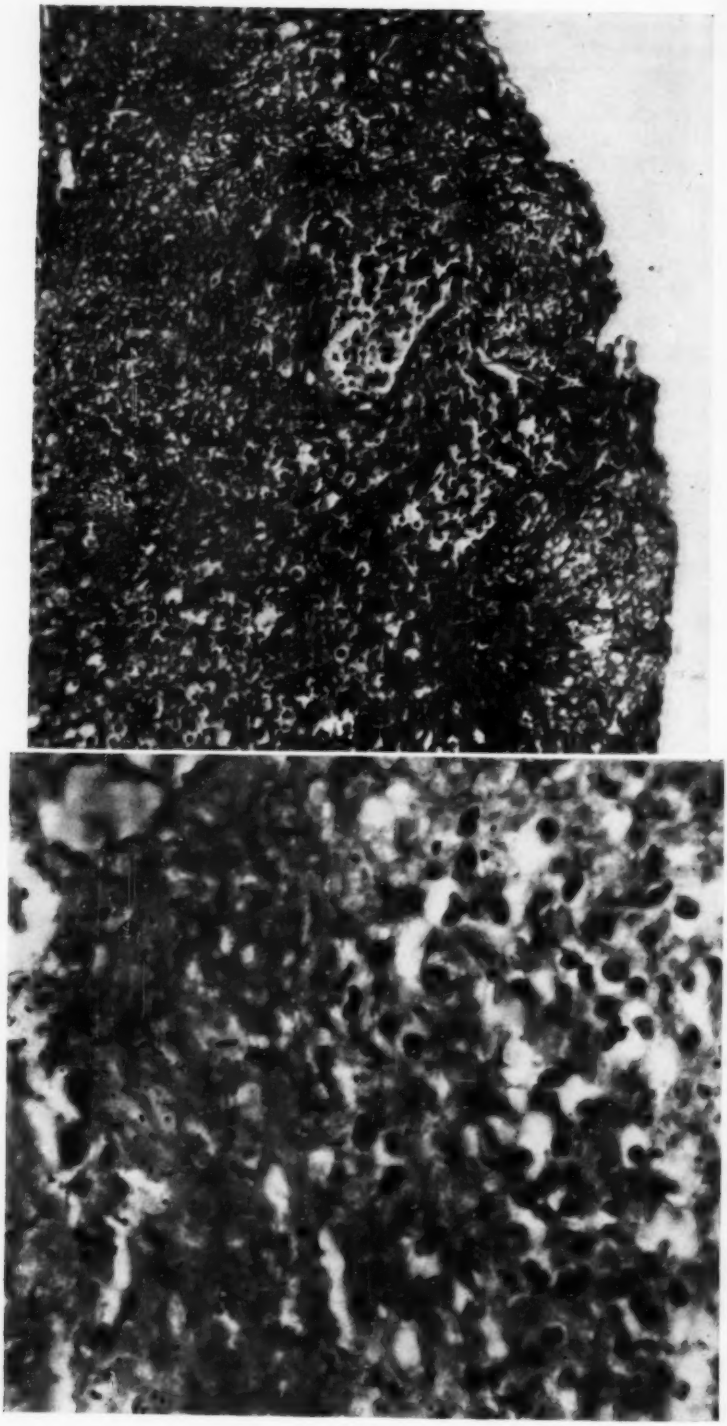
FIG. 11. Dog 131—Stage 5,150 × H & E stain. Antimesenteric border of intestine showing the base of an ulcer. There is a bacterial membrane present overlying many PMN.

FIG. 12. Dog 131—Stage 5,400 × Bacterial stain. This section is from the bacterial membrane showing bacteria, fibrin and debris, and many PMN.



FIGS. 13–14

simple intestinal obstruction. The main causes of the symptoms, signs, and death in simple intestinal obstruction appear to be; 1. Loss of fluid (17, 18); 2. Loss of electrolytes (7, 11, 13, 14, 21, 25); 3. Possible nervous effects of distension (5, 19, 37); 4. Necrosis and ulceration of intestinal wall with possible absorption of bacterial toxins, tissue necrosis toxins, and intestinal content toxins (9, 10, 29, 36, 40). These factors are potentially present in cases of simple intestinal obstruction at all intestinal levels. The loss of fluids and electrolytes is more important the higher the obstruction and the effects of distention and necrosis and ulceration of the intestinal wall with its sequellae are more important in low small intestinal obstruction (Table 2). In general the factors of fluid loss and electrolyte loss manifest themselves first, then distension is superimposed and this is followed by necrosis and ulceration of the bowel. From this series of experiments and from W. E. Abbott's work (1, 2) it appears that some dogs can die from the effects of fluid and electrolyte loss at any level of obstruction. If, however, the dog continues to live, distension will gradually develop followed by necrosis and ulceration of the intestinal wall and later peritonitis. All dogs with high obstruction in our series and some dogs with low obstruction died before distension and bowel damage had time to occur (Table 1). One probable reason that human cases of intestinal obstruction show such a high percentage of ulceration and perforation of the intestine at autopsy is that parenteral replacement of fluid and electrolytes is a relatively easy procedure and is usually carried out well, whereas, relief of distension is almost always more difficult and sometimes impossible. Thus the patients that die of intestinal obstruction usually are treated adequately for fluid and electrolyte loss only to go on to die from the effects of distention and necrosis and ulceration of the intestine.

FIG. 13. Dog 129—Stage 6,150 × H & E stain. This section shows the serosal surface below an ulcer. A local peritonitis is present. There is mesothelial proliberation. Large numbers of PMN are present.

FIG. 14. Dog 129—Stage 6,400 × Bacterial stain. Showing the presence of many bacteria even though no actual perforation of the intestine has occurred. Many PMN are present indicating that the presence of the bacteria is not a postmortum invasion.

Is it possible to prevent this process of necrosis and ulceration of the intestinal wall by giving large doses of penicillin when the distention is not relieved? Previous experiments on dogs with isolated loops showed that this process can be prevented or delayed in most cases by huge prophylactic doses of penicillin (16). However, studies using large intramuscular doses of penicillin in dogs with simple intestinal obstruction must be carried out before any claims can be made as to its value in such cases.

CONCLUSIONS

1. The lower the obstruction the greater is the incidence and degree of hemorrhage, necrosis and ulceration of the intestinal wall at autopsy.
2. The normal intestinal bacteria acting upon tissue whose resistance has been lowered by ischemia due to distension, are responsible for ulceration of the intestinal wall that occurs in simple intestinal obstruction.
3. The lower the obstruction, the greater is the degree of the distension of the intestine at autopsy.
4. The lower the obstruction, the greater is the degree of kinking of the intestine with the resulting formation of the isolated intestinal loops.
5. The lower the obstruction, the less is the concentration of activated pancreatic juice of the intestinal content just above the site of obstruction at the time of death.
6. The lower the obstruction, the greater is the incidence of positive peritoneal and heart blood cultures found at autopsy.
7. If dogs with simple intestinal obstruction are allowed to drink water *ad libitum* the well-established concept that the higher the obstruction, the shorter the survival time, no longer holds true. Instead it is found that dogs with high intestinal obstruction live longer than dogs with low intestinal obstruction.

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THE RENAL CLEARANCE OF THIOSULFATE IN MAN[1]

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WITH TECHNICAL ASSISTANCE OF MARGOT ROBINSON AND MARION BIRMINGHAM

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There have been many studies in the past on the excretion of thiosulfate and its use as a measure of renal function, based on analysis of urine alone. Recently Gilman et al have determined the mechanism of thiosulfate excretion in the dog by analysis of serum and urine (1). They found that the clearances of creatinine and thiosulfate were identical and, therefore, concluded that thiosulfate clearance measures glomerular filtration in the dog.

The purpose of this study was to establish the mechanism of excretion of thiosulfate in the human kidney by the simultaneous measurement of inulin and thiosulfate clearance.

CHEMICAL METHODS

1. *Urine.* Thiosulfate in urine was determined by what we designate the 'direct' method. As large an aliquot of urine as possible is used (2 to 10 cc.) and made alkaline with a few drops of one normal NaOH (one drop of 1% phenolphthalein indicator). Potassium iodate, 25 cc. of .01 normal solution is added. Then 2 cc. of fresh 10% potassium iodide are added, followed by 2 cc. of 2.0 normal hydrochloric acid. The liberated iodine is titrated immediately with a .01 normal thiosulfate solution which has been standardized against 25 cc. of exactly .01 normal potassium iodate solution. (.3567 grams of potassium iodate per litre.) A few drops of 1% fresh clear starch solution are used as indicator.

Reactions involved:

$$\text{I}\quad KIO_3 + 5KI + 6\,HCl = 3I_2 + 6KCl + 3H_2O$$

$$\text{II}\quad 2Na_2S_2O_3 + I_2 = Na_2S_4O_6 + 2NaI$$

[1] Work supported in part by the Life Insurance Medical Research Fund.

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In this reaction 1 cc. of .01N thiosulfate equals 1 cc. of .01N iodate; calculation of urine concentration in milligrams per cent is:

$$\text{Standard titration} - \text{unknown titration} \times 1.58 \times \frac{25}{\text{st'd tit.}} \times \frac{100}{\text{vol. of urine aliquot}}$$

2. *Serum.* Thiosulfate in serum was determined by the 'indirect' reaction in which 1 cc. of .01N thiosulfate equals 8 cc. of .01N iodate. This reaction is thus eight times more sensitive than that used in the 'direct' method and suitable, therefore, for the determinations of the relatively low concentration of thiosulfate in serum.

Proteins are precipitated by adding 3 cc. of serum to 21 cc. of water. Then 3 cc. of one third normal sodium tungstate and 3 cc. of exactly one third normal sulfuric acid are added and mixed. After standing ten minutes a clear supernatant should be obtained on centrifugation. An aliquot of 10–20 cc. of supernatant is added to 10 cc. of .01 normal potassium iodate. *First*, hydrochloric acid is added (2 cc. of 2.0 N. solution) and the mixture is allowed to stand at least five minutes. *Second*, 2 cc. of fresh 10% potassium iodide solution are added and the liberated iodine is titrated with 0.01N thiosulfate solution standardized against 10 cc. of exactly 0.01N KIO_3.

Reactions involved:

$$\text{I} \quad 2KIO_3 + Na_2S_2O_3 + 2HCl = Na_2SO_4 + K_2SO_4 + 2ICl + H_2O$$

$$\text{II} \quad 2KI + 2ICl = 2I_2 + 2KCl$$

$$\text{III} \quad 2KIO_3 + 10KI + 12HCl = 6I_2 + 12KCl + 6H_2O$$

$$\text{IV} \quad 2Na_2S_2O_3 + I_2 = Na_2S_4O_6 + 2NaI$$

In the first reaction one mol. of thiosulfate reduces two mols. of iodate. Since two mols. of iodate result in the liberation of 12 I on the addition of iodide (reaction III), one would expect to find a disappearance of 12 I by the final titration (reaction IV). However, in the first reaction 2 ICl are produced which result in the liberation of 4I on the addition of iodide, so that the final titration shows a disappearance of 8 I for every thiosulfate which reacts with KIO_3. Thus the net gain in sensitivity is eight fold over the "direct" reaction used for urine.

Calculation of serum concentration in milligrams per cent is:

$$\text{Standard titration} - \text{unknown titration} \times \frac{1.58}{8} \times \frac{10}{\text{St'd tit.}} \times \frac{100 \times 10}{\text{cc. of filtrate aliquot used}}$$

Evidence for the accuracy of these methods has been given by Gilman et al. (1).

A method was developed for determining thiosulfate in 0.2 cc. of serum. Precipitation was carried out with 16 cc. of water, 2 cc. of 1% tungstate and 2 cc. of $\frac{1}{18}$ normal sulfuric acid. The reaction and the titration were carried out in exactly the same steps except that .001 N

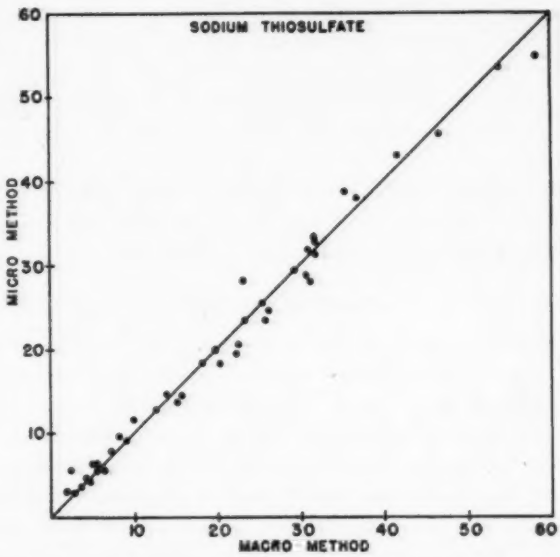

FIG. 1. The average of duplicate thiosulfate determinations in mgm. % on the same sera using 3 cc. of serum (macro) and 0.2 cc. of serum (micro). Standard deviation of the differences between the methods was 0.78 mg.% (total of 41 determinations). The blank values were done also by the micro and macro methods and subtracted from each total determination. Thus the differences represent the sum of error in the blank and in the total thiosulfate determinations.

potassium iodate and .001 N thiosulfate were used. Figure 1 compares the results of the macro and micro methods on samples of the same sera.

In serum, there is an appreciable blank titration for which blood must be drawn before the injection of thiosulfate. In 27 determinations the average serum blank, concentration was 4.18 mg. % (range

2.18 to 8.50). The higher values are usually found in uremic individuals.

In urine there is also a small blank titration which causes no significant error. In 25 determinations the average rate of excretion of blank substances was 0.605 mg./min. (range .05–2.0). At least part of the urine blank is due to substances in urine which react slowly with iodine. The amount of blank titration thus varies with the amount of iodine present and the duration of the titration. The titration is not always directly proportional to the volume of urine used. Because the urine blank is a low and variable value, it has been neglected in the calculation of clearances. If the urine blank is used it should probably be determined by the addition of blank urine to urine containing thiosulfate.

Serum and urine inulin were determined by the method recommended by Goldring and Chasis (2) except that proteins were precipitated by an acid zinc sulfate solution (Somogyi).

CLINICAL METHODS

Simultaneous clearances of thiosulfate and inulin were determined on seven patients with no evidence of renal disease, and on patients with the following diseases: chronic glomerular nephritis, in the subacute, chronic, and nephrotic stages; nephritis due to sulfonamide; pyelonephritis; polyserositis; hypertensive cardiovascular disease with diabetes; sickle cell anemia; coarctation of the aorta; diabetes with nephrosclerosis. The patients were fasting in the basal state. 600 cc. of water was given on the night before the test and 300 cc. again in the morning. Collection of specimens of blood and urine for blank determinations were made immediately before injection of inulin and sodium thiosulfate.

First, ten grams of inulin were injected intravenously as a 10% isotonic solution in about ten minutes.[3] Next, sodium thiosulfate[4] was given intravenously as a 10 to 15 per cent solution during a ten to fifteen minute period.[5] The dosage was roughly one gram per 10 lbs.

[3] Supplied by courtesy of William R. Warner and Co. Inc., New York.

[4] Sodium thiosulfate (Sulfactol) supplied by courtesy of Mr. Lucas of Winthrop Chemical Co., Baltimore.

[5] Mixture of inulin and sodium thiosulfate solutions causes precipitation of inulin.

of body weight, not exceeding a total of 15 grams. After the end of the thiosulfate injection, a period of fifteen minutes was allowed for circulation and diffusion into body fluids. Blood samples were taken from the arm opposite the one into which the injections had been made. Urine was collected from the bladder by a catheter in most cases, and the bladder was washed out with twenty cc. of sterile water and air to insure complete collections.

From three to five blood samples and from three to eight consecutive urine collections were made in the course of the 60 to 120 minutes following the injection of inulin and thiosulfate. Serum and urine were analyzed in duplicate as above, and the clearances for each substance were calculated in the usual way, using the serum level obtained graphically at the mid-point of each urine collection period.

Single injections of thiosulfate and inulin for the determination of clearances offer several advantages over the usual technic of maintaining constant serum levels by continuous infusions. A single injection eliminates some of the equipment and difficulty in maintaining a constant drip. In every case after a single injection, the serum level of thiosulfate follows an accurate logarithmic relationship with time. A typical experiment is illustrated in Figure 2. The consistent direction of the serum concentration makes fewer determinations necessary; and it reveals stray technical errors. Also the determination of clearance with a falling serum level shows that clearance is independent of serum concentration over a wide range in every patient. Finally the slope of the line describing the fall in serum concentration may be used to gain information about the distribution of the substance in body fluids, and about mechanisms of removal from the serum other than excretion by the kidney. (3)

The serum level of inulin apparently requires a longer time to stabilize than of mannitol or thiosulfate probably due to a slower rate of diffusion from serum to extravascular fluid after the single injection.

The possible disadvantages of single injections are that the infusion of concentrated solutions over a short period in order to attain an initial high concentration may be more likely to cause toxic reactions and shifts of fluid in the body. Also the duration of the experiment is limited to a minimum of one to two hours in patients with normal kidneys, since the serum concentration is too low thereafter for accurate determination of clearances.

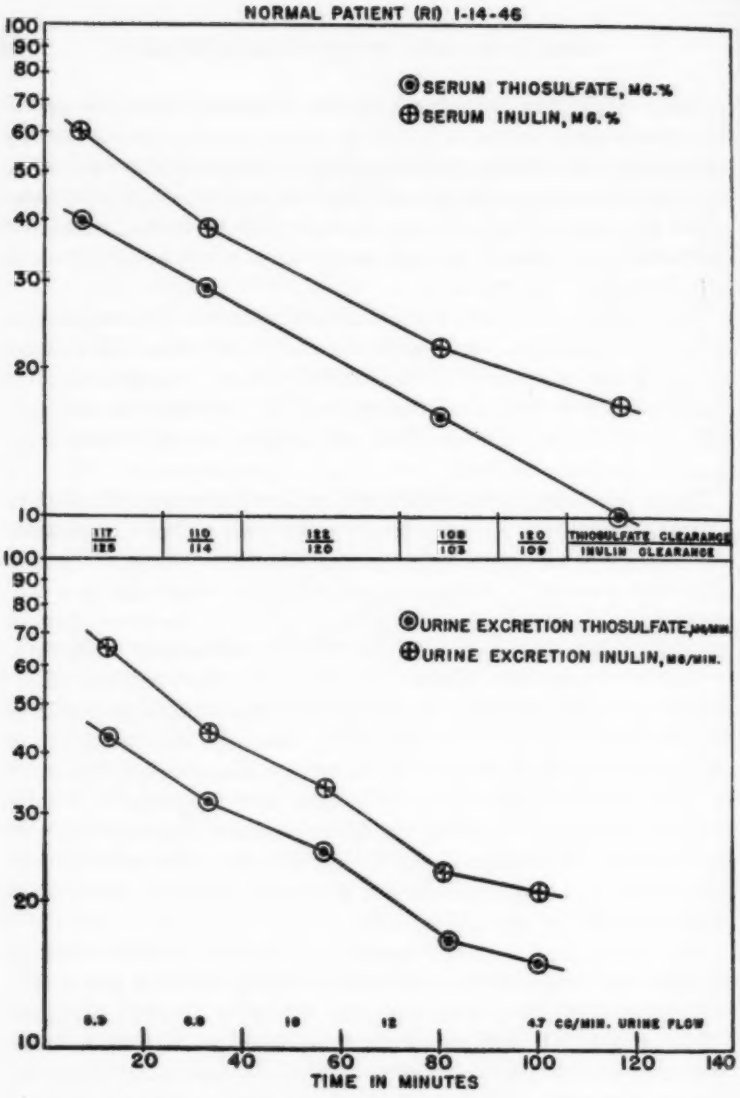

FIG. 2. TYPICAL EXPERIMENT ON A NORMAL PATIENT SHOWING LOGARITHMIC RELATIONSHIP OF SERUM THIOSULFATE CONCENTRATION TO TIME AFTER A SINGLE INTRAVENOUS INJECTION

Serum inulin concentration and the rate of excretion of inulin and thiosulfate are represented. The clearances were independent of serum concentrations and marked changes in urine flow.

RESULTS

In all patients the logarithm of serum thiosulfate concentration followed a straight line with time as illustrated in Figure 2. The inulin concentration showed a slower and slightly curved fall. The

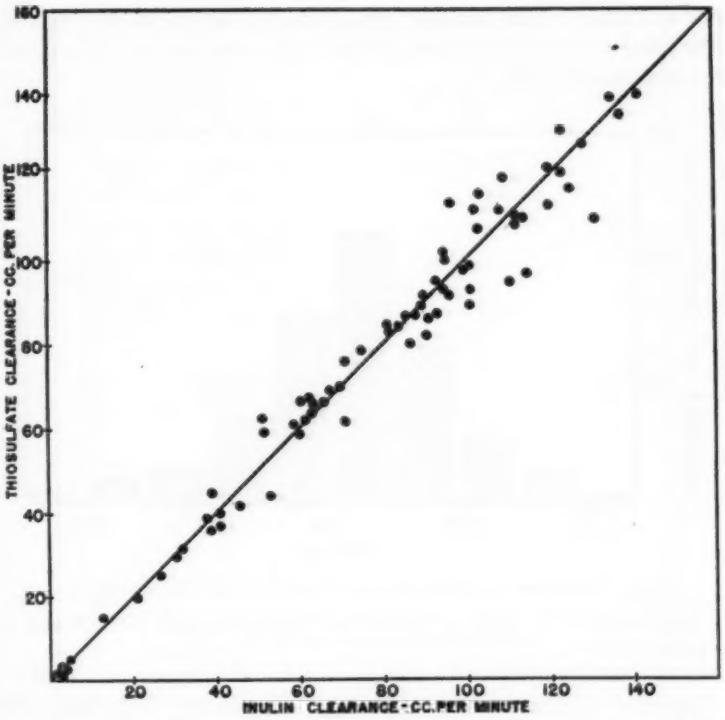

FIG. 3. All the clearances of thiosulfate and inulin in cc. per minute are plotted with the line representing the ratio of unity. All but 12 of the 73 ratios of thiosulfate to inulin clearance fell within the range of 0.90 to 1.10.

rates of excretion of inulin and thiosulfate were parallel to their serum concentrations except when errors in urine collection were made. In other words, the clearances of thiosulfate and inulin were independent of serum concentration. Whenever an error in urine collection was made, the ratio of thiosulfate to inulin clearances remained within

the same limits; none of the clearances were omitted from the chart. The serum thiosulfate concentrations varied from 60 to 6 mg. %, but this range of concentration was not covered in all patients since the serum levels fell at different rates and the initial levels varied.

Urine flow varied markedly in many experiments as illustrated inthe case in Figure 2 where the flow varied from 4.7 to 16.0 cc. per minute. The relationship of thiosulfate to inulin clearance was not affected by changes in urine flow.

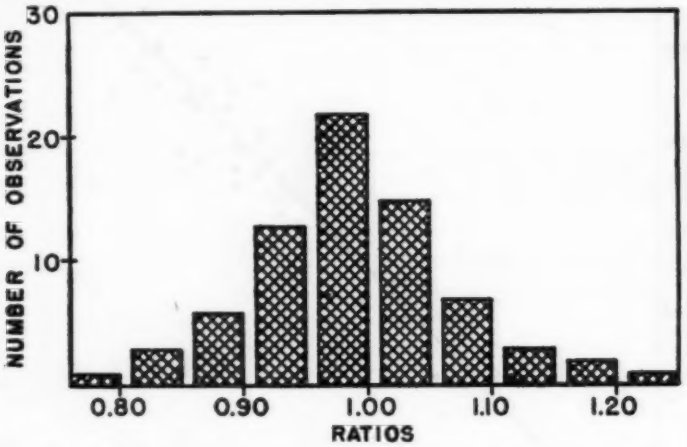

FIG. 4. SHOWING THE DISTRIBUTION OF THE RATIO DETERMINATIONS

The average of the ratios of thiosulfate to inulin clearance was 0.99 with a standard deviation of 0.08.

Figure 3 represents the relationship between the thiosulfate and inulin clearance in every determination on all patients. Complete equality of thiosulfate and inulin clearance is represented by a ratio of unity. The average of the ratios for all determinations on patients was 0.99 with a standard deviation of 0.08 (total of 73 values). Figure 4 shows the distribution of the ratio determinations.

Figure 5 shows the average value of the clearances on each patient. The average of the ratios of thiosulfate to inulin clearances on each patient was 0.986 with a standard deviation of .06 (total of 15 values).

Since thiosulfate is apparently excreted in the same manner as inulin or mannitol, it is possible to obtain some knowledge of the distribution of thiosulfate in the body, and of the extent of destruction in the body. According to previous work with mannitol (3) the slope of the serum curve (S) after a single injection is the ratio of the clearance of the

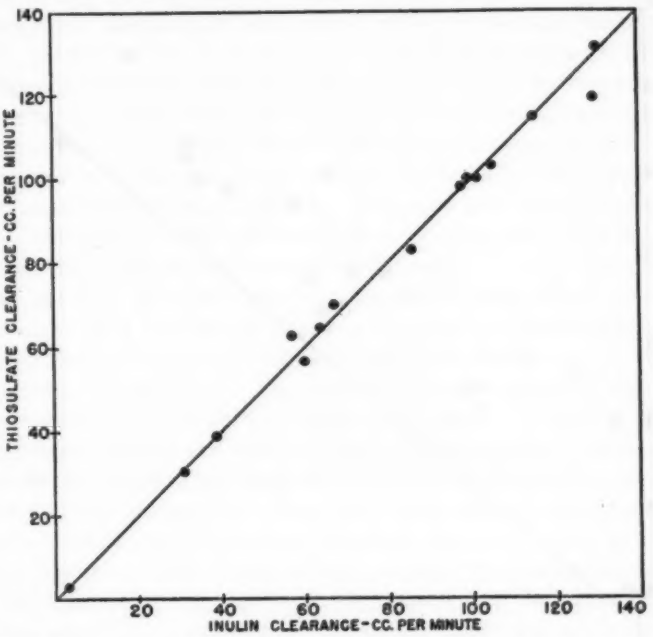

FIG. 5. The averages of the clearances on each patient are plotted with the line representing a ratio of unity. The average of the ratios was 0.986 with a standard deviation of 0.06.

substance (C) to the volume (V) in which it is distributed, i.e. $S = \frac{C}{V}$. Gilman et al. have used these relationships in dogs, and have calculated that thiosulfate is distributed in the extracellular fluid. They find also that some thiosulfate disappears and cannot be recovered in the urine.

Figure 6 shows the slope of the serum thiosulfate curves in each patient in relation to the clearance per unit surface area. The relation

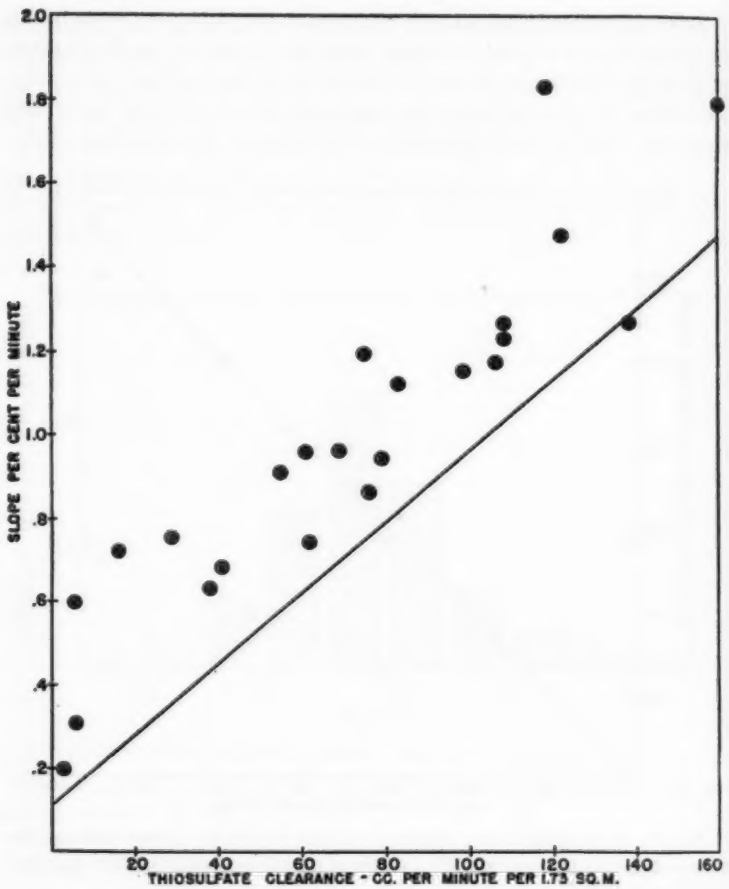

FIG. 6. The slope of the serum thiosulfate concentration in per cent per minute is plotted against the average clearance of thiosulfate for each patient in cc. per min. per 1.73 sq. m. of surface area. The line is the relation of the slope of serum mannitol concentration to its clearance after single intravenous injections (3). The higher rate of disappearance of thiosulfate is probably due to destruction in the body.

of the slope of mannitol curves to the mannitol clearance per unit surface area (3) is also represented. Differences between serum

mannitol and thiosulfate slopes will depend on factors such as destruction of thiosulfate, and differences in the volumes in which they are distributed.

DISCUSSION

The criteria for establishing thiosulfate as a measure of glomerular filtration rate seem to have been fulfilled within the limits of the errors of the determinations in both normal and diseased kidneys. The clearance of thiosulfate appeared to be independent of serum concentrations over the range employed in these experiments. The average clearance rates as measured with inulin are nearly identical to those determined by thiosulfate, and no effect of change of urine flow or serum concentration was observed. Clearances at a constant serum level of thiosulfate maintained by infusion have not been done, but it seems unlikely that the results would be different.

The fact that the disappearance of thiosulfate from the serum was more rapid than the disappearance of mannitol or inulin indicated either a smaller volume of distribution or that destruction of thiosulfate was taking place. The increased rate of disappearance is evident when excretion by the kidney is minimal. If the increased rate of disappearance were due to a smaller volume of distribution, the slopes of the curves would approach identity when excretion by the diseased kidney is negligible. From the data in Figure 6 it is apparent that more rapid disappearance of thiosulfate than of mannitol occurs at every rate of excretion by the kidney. It has been shown previously (1) that thiosulfate is distributed in the extra-cellular fluid in the dog and that slow destruction occurs. The data in Figure 6 are compatible with the interpretation that in the human the volume distribution and extra renal loss of thiosulfate are similar to those found in the dog.

TOXICITY OF SODIUM THIOSULFATE

Litwins et al. (4) commented on the variety of diseases for which sodium thiosulfate has been administered, and the difference of opinion concerning the therapeutic merits. However, there was unanimity of opinion regarding its lack of toxicity. Litwins from human experiments and Goldblatt (5) from observations on dogs agreed that intravenous injection may cause undesirable side effects due to the following factors: too concentrated a solution; too rapid an injection; too large a

dose. Another factor which seemed of great importance was the age of the solution. Goldblatt found that toxicity of a solution became manifest after a period of forty-eight hours following preparation. He prepared a non-toxic solution from alcohol precipited C.P. sodium thiosulfate. Litwins stated that the "slow intravenous administration of 200 cc. of a 12% solution evoked no sensations." "There may be nausea, or more rarely vomiting from concentrated solutions after 500–1000 grains, too rapid injection, from old solutions, or when the injection is given after fasting."

According to the experience of others, the dosage of sodium thiosulfate used in our experiments was non-toxic. However, nausea and vomiting occurred in seven of the twenty-six patients receiving injections. Vomiting occasionally occurs in fasting patients who have been forcing fluids. Patients who are in azotemia or uremia are likely to have nausea or vomiting. The emotional excitement of the procedure is probably also a contributing cause. In no case was the reaction severe or protracted.

It seems likely that one of the important causes of nausea and vomiting was the age of the sodium thiosulfate. A fresh preparation with a concentration not above 10% should be given slowly. Whether deterioration of alcohol precipitated sodium thiosulfate in ampoules can be prevented is now under investigation. A dosage and rate of administration which causes no nausea needs to be determined.

In order to recommend sodium thiosulfate for general use to measure glomerular filtration rate, the injection should not cause changes in filtration rate or renal blood flow. Preliminary observations show that injections of thiosulfate cause no change in inulin and in para-aminohippuric acid clearances, but more studies are necessary to establish this beyond question.

Inasmuch as inulin, mannitol and thiosulfate are excreted by the kidney in the same manner, the question arises whether the use of thiosulfate affords any advantage in the determination of glomerular filtration in humans. The ease and accuracy of analysis for thiosulfate is in contrast to the more difficult and lengthy procedures for the determination of mannitol and inulin. Thiosulfate has been found to be stable in urine and in filtrates over periods of several days. Provided the anion is non-toxic and causes no side effects on filtration

rate and renal blood flow, it should prove a most useful agent for the determination of glomerular filtration. Moreover, thiosulfate is the only anion thus far known which is not reabsorbed by the tubules, and can be given in large amounts.

The excretion of an anion at the rate of glomular filtration obligates the simultaneous excretion of cation. Preliminary observations have indicated that a study of the partition of urinary base excreted with $S_2O_3^-$ may aid in the interpretation of fundamental changes in the excretion pattern of electrolytes by the normal and diseased kidney.

SUMMARY AND CONCLUSIONS

Methods of determination of thiosulfate in serum and urine are described.

Simultaneous clearances of thiosulfate and inulin were determined in patients with normal and diseased kidneys after single intravenous injections.

After a single intravenous injection of sodium thiosulfate, the logarithm of serum concentration is a straight line plotted against time.

The ratio of thiosulfate clearance to inulin clearance was 0.99 on the average, with a standard deviation of 0.08.

The ratio of thiosulfate to inulin clearance was independent of changing urine flow and serum concentration within the range obtained in every patient.

Comparison of the slope of the falling serum thiosulfate concentration with the slope of mannitol concentration after single injections reveals that excretion by the kidney does not account for the disappearance of all of the thiosulfate from the serum.

Nausea and vomiting were encountered in a few instances from intravenous injection of sodium thiosulfate. This reaction is thought to be due in part to the age of the preparation used. The speed of injection and the concentration of the solution may be responsible.

The effect of injection of sodium thiosulfate on filtration rate and renal blood flow should be determined.

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DIFFERENCES IN THE ACTION OF CRYSTALLINE AND NON-CRYSTALLINE PREPARATIONS OF ESTRIOL

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Several investigators have reported differences in the biological activity of crystalline steroid hormones as compared with highly purified but non-crystalline hormones prepared from natural source-material. Such differences have been found in the case of androgens (1), estrogens (2), adrenal cortical hormones (3, 4) and progesterone (5). The following experiments were intended to explore the same question with respect to estriol. The rhesus monkey (Macaca mulatta) was used as a test animal because of the high responsiveness of its secondary sex organs to estrogenic stimulation.

The effects of crystalline synthetic estriol, furnished by Dr. E. Schwenk of the Schering Corporation, were compared with those of purified estriol prepared by the author from pooled human urine. After acid hydrolysis, the phenolic fraction was distributed between benzene and 0.3M Na_2CO_3 (6) and the carbonate fraction was treated again with benzene before final extraction with ether. The potency of both the crystalline and the non-crystalline preparations was determined by bioassay using spayed rats.

Three adult female rhesus monkeys, oophorectomized for several years, were injected subcutaneously each day for a standard period of 10 days with 75 rat units of the crystalline estriol. Each dose was dissolved in one c.c. of sesame oil. The effect of the treatment was followed by daily vaginal smears stained by Shorr's method (7) and the appearance of vaginal bleeding was determined by microscopic study of lavage specimens as well as by macroscopic observation.

The injections of crystalline estriol resulted, as expected, in reddening of the sex skin and atypical cornification of the vaginal cells, but no menstruation-like bleeding occurred after the withdrawal of estriol, during the period of observation dating from three to five weeks in the different animals. The animals were not reinjected until the sex skin and the vaginal smears returned to the castrate condition.

The same three animals injected with the non-crystalline estriol of

human origin, given in the same dose administered in the same way, responded to the hormone just as before by changes in the sex skin and vaginal cells. In addition they exhibited menstruation-like bleeding respectively 10 days and 7 days after the last injection. The duration of flow was (animals in the same order) 2, 4 and 4 days, averaging 3.3 days, which is within the usual limits of estrin-deprivation bleeding in this species.

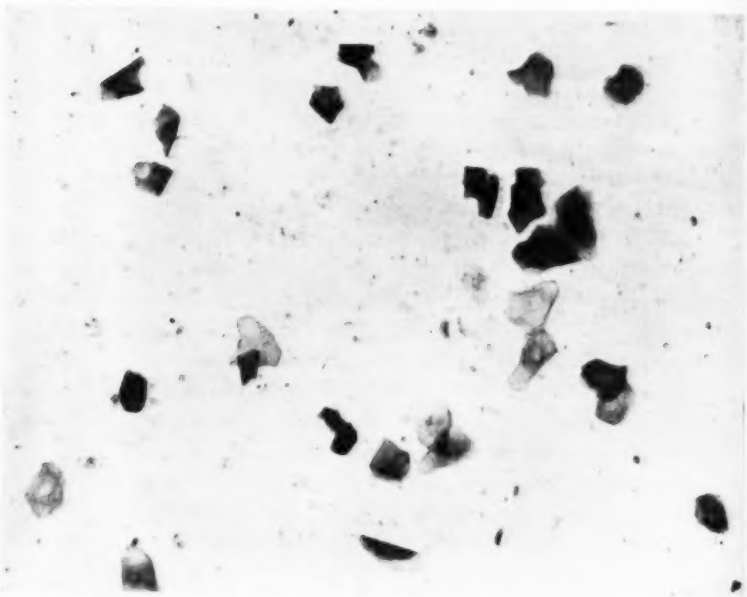

FIG. 1. VAGINAL SMEAR OF CASTRATE MONKEY TREATED WITH ADRENO-CORTICOTROPHIC HORMONE, SHOWING CORNIFIED CELLS. × 200

DISCUSSION

Several possibilities may be discussed in connection with the factors determining these two different reactions of hormones containing the same amounts of estriol by bioassay.

Contamination of the human estriol by the more potent estrone and estrodiol can be eliminated, since by the method of partition used (6) the contamination will amount at most to 5 per cent, which is far

below the threshold necessary for inducing hormone deprivation bleeding.

A possibility which deserves more consideration is the presence of substances enhancing the activity of the autogenous estriol but lacking in the crystalline preparation. Emmens (9) showed that palmitic acid acts synergistically with estrogens. Smith (10) recently demonstrated that a lactone, an oxidative inactivation product of estrone, induces in the gonadectomized adult male rats the release of gonadotrophic and adrenotrophic factors of the anterior pituitary.

It is plausible to assume that such substances might act by stimulating the adrenal gland to produce supplementary steroid hormones. A mechanism of this sort was considered by Zuckerman (11) as an explanation of the fact discovered by him that periodic uterine bleeding occurred in the oophorectomized rhesus monkey injected continuously with a threshold dose of estrone.

In order to detect an influence of the adrenal glands upon the secondary sex organs, two castrated female rhesus monkeys were injected with 30 milligrams of adrenocorticotrophic hormone daily for ten days. In this case the intensity of the sex skin color was increased by two degrees (according to the scale used in this laboratory, this will indicate a moderate but definite change) and the vaginal smear became "cleaner," that is to say, freer of mucus strands and cell debris, and showed a marked increase of the cornified cells which are stained pink by Shorr's method (fig. 1). This indicates that the adrenal cortex can release hormones affecting the secondary sex organs. Similar, though less definite results were obtained in an unpublished earlier experiment at this laboratory some years ago, using an adrenocorticotrophic extract supplied to Dr. C. G. Hartman by Professor H. M. Evans.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in the Hurd Memorial Hall, December 10, 1945

The Use of Radium in the Aerotitis Control Program of the Army Air Forces. S. J. Crowe.

Aerotitis is due to partial or complete closure of the Eustachian tubes and the resulting inability to equalize the pressure in the middle ear and mastoid cells with that of the surrounding air.

There are several predisposing causes for failure of the Eustachian tubes to function normally, such as inattention or forgetting to carry out the muscular movements that aid in opening the Eustachian tubes, but the primary underlying cause is the common cold, or a subacute or chronic infection in the upper air passages. The inevitable result of infection in the pharynx and nasopharynx in children and young adults is hyperplasia of lymphoid tissue. The mucous membrane of the lateral and posterior walls of the nasopharynx is rich in lymphoid tissue. Hyperplasia of this lymphoid tissue in and around the pharyngeal orifice of the Eustachian tubes makes the patient more susceptible to upper respiratory infection, causes excessive secretion of mucus and thus further interferes with the function of the tubes.

Lymphoid tissue around the Eustachian tubes often is so located that it cannot cannot be removed surgically. For many years we have been irradiating the nasopharynx of children and young adults with impaired hearing, recurrent attacks of otitis, or chronic ear suppuration in order to remove lymphoid tissue and restore the function of the Eustachian tubes. The only symptom in these patients may be slowly progressing impairment of hearing. The onset in civilians is insidious and slow in comparison to the onset of aerotitis in aviation or submarine personnel, but the underlying physical causes are the same. Since the advent of sulfonamides, tyrothricin and penicillin our results have been much improved by using the combination of chemotherapy (locally or systemically) to control infection and radium to remove hyperplastic lymphoid tissue and restore the tubes and their surroundings to as near normal condition as possible.

As the name implies, the primary object of the Aerotitis Control Program was not to treat individuals with the acute stage of aerotitis, but to follow the plan employed in civilian practice for many years: i.e. (1) examine the upper air passages and nasopharynx of large numbers of men in training areas for abnormalities that predispose to upper respiratory infection and ear disorders, and, (2) in combat zones to examine and treat men who had been grounded with aerotitis to try to prevent recurrence on subsequent missions. It is difficult to evaluate the results statistically, because of the difficulty of following the treated men for a long enough period after their treatment had been completed and high-altitude flying resumed.

The results, based on a follow-up of at least one month after completion of the radium treatments, showed that about 80% were improved subjectively and objectively.

The primary object of this paper is to point out that this method of therapy is applicable to dispensary patients and school children. The end result after surgical removal of tonsils and adenoids in children is often unsatisfactory and the indications for this operation must be revised.

Many patients, particularly children, who come to the out-patient department have symptoms referable to hyperplastic or infected lymphoid tissue. For many years we wasted time and energy in examining these patients, but had little to offer as therapy, except operative removal of tonsils and adenoids. Due to lack of beds three-fourths of these patients never received any treatment. Many operated on were not permanently benefitted. During the past six years we have treated about 200 dispensary patients each month with a combination of radium and chemo-therapy, with results far better than we have ever seen before.

If public school children were screened, just as air force and submarine personnel were screened, and those having symptoms, or local conditions that we know will endanger the hearing (or lead to chronic sinusitis, or asthma) are recognized early, while the changes in the ears, sinuses or lungs are still reversible, and treated properly, then the health of the population so far as these maladies are concerned could be decidedly improved. Such a program is not possible when the therapy requires hospitalization and operation, but it is possible and feasable in ambulatory clinics.

The requirements for such a program would be the same as those in the Air Force work—i.e., men trained to examine the ears, upper air passages and especially the nasopharynx with a nasopharyngoscope. Radium applicators are permanent and inexpensive compared to hospitalization and operative therapy. Two men can easily examine and treat 50 children a day, with perfect safety to both children and doctors.

DISCUSSION

Lt. Col. John Bordley: I have had less experience with radon therapy than Dr. Crowe, both here and overseas, therefore I can speak with no such authority. While overseas I saw no pilots who had been treated through the Air Corps program in the United States. Of the group that were seen and treated in the same manner, at the 118th General Hospital, the following observations can be made. Improvement in pilots during combat flying and suffering from aero-otitis media is not so good as that of men in the training centers. The trauma to the middle ear is undoubtedly greater in combat; most of the patients had blood or serum in their middle ears and severely scarred tympanic membranes. Pursuit pilots showed the greatest changes in their ears. Even in the combat group improvement was surprisingly satisfactory. In conclusion, I feel that if the Air Corps had inaugurated Dr. Crowe's program at the beginning of the war, we would have had more pilots in the air, in the combat zones where they were so dreadfully needed. The best time of all to remove eustachian obstruction is in childhood.

Studies on the Electrolyte Disturbance of Infantile Diarrhea. Dr. Daniel C. Darrow, Yale University, School of Medicine.

Recent work has shown that the distribution of body water and electrolyte is is not dependent on exclusion of sodium and chloride from the cells. If all intracellular fluid is like that of muscle, there is about one-sixth as much intracellular sodium as the total sodium in extracellular fluids. Under certain circumstances sodium can replace potassium within the muscle cells. Loss of potassium can amount to about 40 per cent of the total normal content of the muscle. Under these circumstances, the intracellular sodium may be equivalent to about one-third of that in extracellular fluid if all intracellular fluid is like that of muscle.

In studying diarrhea it was assumed that the retentions during recovery measure the losses which have produced the picture of dehydration. In order to determine these losses, the balances during recovery were determined for nitrogen, sodium, chloride, potassium, phorphorus and calcium. These balances were related to the serum concentrations in order to determine the changes in intracellular sodium when it is assumed that all chloride remains extracellular. The balances of potassium and phosphorus were corrected for the balances of nitrogen and calcium. The assumptions for these calculations were that cellular fluids tend to have the relation of nitrogen to potassium and phosphorus that is found in muscle and that the balance of calcium is reflected by a balance of phosphorus as indicated by the composition of bone salts. Six studies of this kind were reported.

In two cases the balance of chloride was greater than the balance of sodium despite recovery from marked acidosis. In these cases the acidosis was apparently produced in part by transfer of a considerable amount of sodium to the intracellular fluids which, during recovery, became extracellular. In all cases the balance of potassium was large—amounting to almost one quarter of the estimated normal content of the body in the most severe case. The changes in intracellular phosphorus were not large in any of the cases studied.

When the cases were treated during the period of fasting with solutions containing only sodium chloride and sodium lactate, sodium was apt to increase within the cells and the deficit of potassium was apt to increase. When potassium chloride, sodium chloride and sodium lactate were used parenterally during the period of fasting, retention of large amounts of potassium was produced.

These findings were used to develop a new system of treatment in which potassium chloride, sodium chloride and sodium lactate are given parenterally in order to replace the electrolyte loss of diarrhea. As demonstrated by clinical trial under the direction of Dr. Clifton Govan, this treatment enables babies to recover from an attack of diarrhea that would be otherwise fatal.

The implications of deficit of body potassium were discussed and it was pointed out that other types of disturbance in electrolyte balance almost certainly involve loss of body potassium which can be favorably influenced by parenteral therapy with solutions containing potassium as well as sodium salts.

The Use of Potassium Chloide in the Treatment of Dehydration due to Diarrhea. CLIFTON D. GOVAN, Jr., Department of Pediatrics, and DANIEL C. DARROW, Yale University School of Medicine.

The recent studies of Dr. Daniel C. Darrow have shown that prolonged or intense episodes of diarrhea lead to large losses of potassium as well as sodium, chloride and water. The loss of potassium is out of proportion to the loss of nitrogen and, therefore, is an important aspect of the disturbance of the electrolyte pattern in infants suffering from diarrhea. The administration of potassium can replace this deficit at a time when food cannot be given without aggravating the diarrhea.

To replace these losses of water and electrolyte in severely dehydrated infants, a solution having approximately the following composition per liter was administered intravenously and subcutaneously:

K	35 mM per liter
Na	122 mM per liter
Cl	104 mM per liter
Lactate	53 mM per liter

The solution was made according to the following formula:

KCl	2 grams
NaCl	3 grams
⅙ molar sodium lactate	250 cc.
Water	500 cc.

During the first 24-hour period, in addition to the use of whole blood and plasma for the treatment of shock, the KCl-NaCl-lactate solution was administered in amounts varying between 70-150 cc. per kilogram of body weight. Sufficient 5 % glucose solution was then given intravenously to make the total fluid intake for the day up to 200-250 cc. per kilogram of body weight. After the first 24 hours further losses of water and electrolyte were attended by the administration of smaller amounts of the KCl-NaCl-lactate solution and glucose.

The parenteral injections of potassium were continued until evidence of dehydration had been overcome and until intestinal absorption appeared normal. When feeding was resumed a mixture of equal parts of skimmed milk, lactic acid milk with 5% dextrimaltose added was given.

As the KCl-NaCl-lactate mixture contained ten times the concentration of potassium found in the extracellular fluids, two precautions were observed. The solution was never administered intravenously more rapidly than 2 cc. per minute and usually was not given until evidence of urine formation was assured. The failure to observe the last precaution resulted in a clearcut instance of potassium intoxication.

The period of observation extended from June to November 1945, during which

time 104 infants were admitted to the Harriet Lane Home suffering from diarrhea. From June to September, 53 of these infants received the conventional form of treatment and 17 died. From September to November, 51 received in addition to the conventional form of treatment, parenteral injections of potassium and only 3 died. Owing to the limitation of beds, only severely ill patients were admitted to the wards, and as a result the severity of the illness of the infants in both groups was comparable. The age of the infants in the two groups was also comparable; at least 80% of the infants in both groups were under 6 months of age.

Of the 3 infants that died in the group receiving parenteral potassium, one was a 25-day-old infant who had had diarrhea for 23 days; another was an infant who died six hours after admission; and the last was a congenital syphilitic who had no diarrheal stools for five days before death, and although he had two loose stools the night he died, diarrhea would not ordinarily be considered the cause of death. Of the first 43 infants treated with parenteral injections of potassium, only one failed to survive. These infants survived during the month of September, when the mortality from diarrhea in Baltimore is usually very high.

The plan of treatment described did not apparently shorten the period of watery diarrhea. However, the infants looked better sooner after this form of therapy was instituted and were able to survive a period of diarrhea that otherwise would probably have been fatal.

DISCUSSION

Dr. Kajdi: In observing these children with Dr. Darrow, I was greatly impressed by the clinical improvement following the use of potassium salts. The return to normal hydration required the administration of much less fluid when potassium was used.

Dr. Wilkins: Due to the prevalence of infantile diarrhea and the late stages in which these children are brought to the hospital, we have always had a distressingly high death rate from this disease. Dr. Gamble's important studies on the loss of extracellular fluid were followed by a great improvement in the results of treatment, and our attention has been concentrated on this. Now Dr. Darrow's painstaking work has brought out something which we had all missed and which has produced a great improvement in therapy. We used to save three out of four of these children with treatment directed toward replacement of extracellular fluid. The fourth child would go on and die without any obvious explanation. Improvement in intravenous technique and the use of transfusion failed to improve the results until Dr. Darrow pointed out the importance of intracellular electrolyte replacement. Dr. Darrow is so modest that I do not want you to go away with the impression of just a lot of figures. This is really a great therapeutic advance. Such good results could not have been obtained except for the careful detailed care which was given these patients by Dr. Govan.

Dr. Josephs: Dr. Darrow's findings are very important in the treatment of diarrhea in children and also might be applied to other conditions with similar

effects on the cellular electrolytes. This is an advance as important as the use of base and fluid in acidosis. I particularly admire Dr. Darrow's confidence in his chemical examinations. Is there any other way to evaluate the deficit of potassium except through balance experiments?

Dr. Darrow: We have used the complicated study of balances in these children because blood levels are not a reliable index of the changes. The serum potassium is not always low, even in the presence of a severe potassium deficit. I think we can best be guided by the child's condition when balances are not available. Babies waste a lot of potassium during the early stages of treatment. Some caution must be used in the administration of sodium since sodium therapy further depletes cellular potassium.

I want to thank Dr. Park particularly for letting me try our ideas at the Harriet Lane Home where many more cases are available than we could have found in New Haven. I want to acknowledge also the splendid cooperation of Dr. Govan and the house staff who were so helpful in carrying out the complicated procedures involved. My thanks are also due to the nurses whose help with the collections was invaluable. Dr. Kajdi opened his laboratory to us and was most helpful in every way.

Dr. W. M. Clark: Dr. Darrow's work is an inspiring development, not only in the clinical application but also in our thinking about electrolyte replacement. We have known for a long time that sodium is not stuck permanently outside of the cell or potassium inside, as we originally were taught. Now that we know that the exchange of these ions across the cell membrane is so important, I wonder whether Dr. Darrow could suggest any explanation of the constraints that cause the unequal distribution under normal conditions.

Dr. Darrow: That is your job, Dr. Clark.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal)

Atlas of Surgical Approaches to Bones and Joints. By TOUFICK NICOLA. Illus. 218 pp. $5.00. *The Macmillan Company, New York, New York,* 1945.

A visual image is so much clearer and more lasting than any description that an "Atlas of Surgical Approaches to Bones and Joints" is an extremely valuable addition to orthopedic surgery. The author makes no mention of pathology and refers to no orthopedic operation but illustrates with 227 pen and ink drawings executed by himself the procedure in exposing each bone and joint, from an outline of various skin incisions to layer-by-layer approach to the operative site. The book is truly an atlas with no more word description than to name the structures and describe the important ones to avoid.

While each surgeon has developed his own modification of standard operative procedures, this book affords a ready reference to review the surgical anatomical relationships of vital structure before attempting to open a joint with which he is not completely familiar. One can appreciate the time consumed in the dissections necessary to prepare the illustrations but the author is amply rewarded by his vivid presentation. R. E. L.

A Bibliography of Visual Literature 1939–1944. Compiled by JOHN F. FULTON, PHEBE M. HOFF and HENRIETTA T. PERKINS. 115 pp. $3.00. *Charles C Thomas, Springfield, Illinois,* 1945.

This bibliography which was prepared by John F. Fulton, Phebe M. Hoff, and Henrietta T. Perkins, for the Committee on Medical Research originated in a request for such a classified bibliography by the British Air Ministry. Although it was designed primarily on the basis of military and naval usefulness it is equally valuable to ophthalmologists engaged in civilian practice.

Over three thousand references are included and these have been found in a wide variety of Journals other than ophthalmological—Engineering, Industry, and Physics, to mention only a few sources which ophthalmologists would likely overlook. The references are arranged under the following headings: anatomy, physiology and psychology, visual examination and testing (including methods and instruments) correction of ocular defects in military personnel, ocular trauma, goggles and ocular protection, illumination and visibility. F. B. W.

Diagnosis and Management of Peripheral Nerve Injuries. By ROBERT A. GROFF and SARA JANE HONTZ. Illus. 188 pp. $8.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1945.

This little book was presented by the authors "to provide the physician and physical therapist with a concise text" for the understanding, identification and management of injuries to the peripheral nerves. It is addressed especially to those who have had little or no experience in the handling of these lesions.

The volume is arranged in two parts, of which Part One is devoted to a general discussion of injuries to peripheral nerves, with advice leading to immediate recognition and effective management, even through the post-operative period. Part Two is devoted entirely to a profusely illustrated outline of peripheral and cranial nerve function which appears to be a good, practical aid in localization of a nerve injury.

On the whole, this book will undoubtedly be of greatest value to the house officer confronted with a fresh peripheral nerve lesion in the average hospital accident room. To him it should be a ready reference guide. F. J. O.

Digitalis And Other Cardiotonic Drugs. By ELI RODIN MOVITT. 1st Ed. 204 pp. $5.75. *Oxford Medical Publications, New York, New York,* 1946.

This book is an excellent review of a subject matter which is of great importance especially to the internist. The arrangement of the material with discussion of the historical aspect, source, chemical structure of the drugs, their clinical application is a very desirable one. The text is not overcrowded with illustrations.

The author has drawn freely from the literature for his material and the numerous references make this a valuable reference in addition.

This text is recommended whole heartedly to the student and internist alike. The appendices are very useful in view of the variability of dosages of cardiac glycosides and their nomenclature. K. H. B.

Electrocardiography in Practice. By ASHTON GRAYBIEL and PAUL D. WHITE. 2nd Ed. Illus. 458 pp. $7.00. *W. B. Saunders Company,* 1946.

This second edition of Dr. Graybiel's and Dr. White's text is one which can be recommended most highly to anyone interested in electrocardiography. The purpose of the text is certainly borne out in this present edition. The section on precordial leads is a most useful and desirable addition. The stress laid upon proper appreciation of the broad range of normal patterns is certainly to be commended.

The division of this volume into five parts: (1) essential physiologic principles and technic, (2) range of normal patterns, (3) disorders of rhythm, (4) electrocardiographic changes and patterns in various diseases which affect the heart, and (5) new series of "test" electrocardiograms is a very good one. The four new tables which discuss effects of the "indifferent electrode," disorders of rhythm, the changes in the electrocardiogram in various diseases affecting the heart, and the changes resulting from the administration of various drugs and effect of various physiologic influences are certainly very useful additions. K. H. B.

Diseases of the Nose, Throat and Ear. Edited by CHEVALIER JACKSON and CHEVALIER L. JACKSON. Illus. 844 pp. $10.00. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1945.

This textbook presents the various phases of otorhinolaryngology and bronchoesophagology in very readable and practical form. Each article is written by an authority on the subject and is followed by a bibliography. Four hundred and fifteen pages are devoted to diseases of the ears, nose, nasal accessory sinuses, mouth and pharynx, and three hundred and thirty-six pages to the larynx, trachea, bronchi, and oesophagus. There follows a section dealing with general considerations, including chemotherapy, aviation oto-laryngology and anesthesia both local and general.

The newer operative procedures are given in detail and understanding is facilitated by a number of excellent illustrations. On controversial subjects the views of two or more contributors are presented. This book will prove most valuable to students, general practitioners and specialists who are interested in diseases of the ears, nose and throat. J. J. C.

Essays in Biology in Honor of Herbert M. Evans. 687 pp. $10.00. *University of California Press, Los Angeles, California,* 1943.

This book includes a series of 48 essays compiled by Thomas Cowles in honor of the 60th birthday of Herbert Evans. The essays cover a variety of subjects which are of interest to clinicians, biologists and medical historians, and should be attractive to those who are interested in the broad fields of medicine, and to those who have had contact with Dr. Evans. The printing and reproduction of figures is excellent and reflects credit on the University of California Press. H. N. H.

New Directions in Psychology Toward Individual Happiness and Social Progress. By SAMUEL LOWY, $3.00. *Emerson Books, Inc., N. Y.,* 1945. 194 pp.

The author, a psychoanalyst of wide experience, has expressed in semi-popular form a series of somewhat disjointed reflections upon the social issues encountered in his professional work. The result is a somewhat scattered, but urbane and benevolent, essay heading up to the general proposal that the power of the State be employed for "inducing people and their communal leaders to assume a socially beneficial attitude." In his suggestions on general reform he argues against "the even distribution of means" as the road toward true social improvement. He proposes rather "the more even distribution of burdens and pains" as "the desirable magic formula." This "implies rather less pressure on the poor and uninfluential, the abolition of the continuous fear about elementary needs of the individual and his family. . . . What is also necessary is the maximum of knowledge on vital problems of psychology and sexual character; the granting of all available means of public assistance, to forestall the development of an advanced neurotic make-up or physical disability; and also an appropriate share for everybody in the beauties of civilization and nature."

It is the reviewer's impression that the author bases his proposals upon a too limited and passive view of human nature, including a somewhat unrealistic

faith in the benevolence of bureaucracy; yet he offers many stimulating and penetrating comments upon the unconscious forces operating in social systems.

J. C. W.

Nursing in Clinical Medicine. By JULIUS JENSEN and DEBORAH MCCLURG JENSEN, 2nd Ed. Illus. 827 pp. $3.50. *The Macmillan Company, New York, New York,* 1945.

This is a text and reference book written primarily for student nurses but it should be useful as reference for graduate nurses, social workers, occupational therapists and hospital dietitians. In addition to general medicine, sections on diseases of the skin as well as acute communicable diseases are included. Etiology, symptoms, course and complications, treatment, nursing care and public health and social aspects of the various disease conditions are given in clear, concise form. The illustrations are well selected and include x-rays, photographs of pathological specimens and of patients, line drawings and pictographs which make the presentation of statistical material more interesting to the average reader. There are references for collateral reading and review questions and topics for discussion following each unit. M. S.

Pathology in Surgery. By NATHAN CHANDLER FOOT. Illus. 511 pp. $10.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1945.

This book, written by the well known Professor of Surgical Pathology at the Cornell University Medical College, is an excellent atlas of surgical pathology. It especially emphasizes microscopic pathology and a number of the 400 illustrations are very fine photo-micrographs by Mr. Robert Waldeck. Certain of the gross specimens are portrayed in color and the reproductions of these undoubtedly do not do justice to the original artist's renditions. The outline of the subject includes several chapters on general surgical pathological problems, including the subjects of inflammation, wound healing, and general remarks on tumors. The various anatomic systems of the body are then considered serially in detail and not only the general surgical aspects of the subject are discussed but urological and gynecological and neurosurgical pathologic specimens are discussed in detail. A section on laboratory methods and the conduct of a surgical pathologic laboratory serves as a useful adjunct of the general exposition of the subject. H. N. H.

Plaster of Paris Technique in the Treatment of Fractures and other Injuries. By T. B. QUIGLEY. 107 pp. $3.50. *The MacMillan Company, New York, New York,* 1945.

"Plaster of Paris Technique in the Treatment of Fractures and other Injuries" is a short volume of 104 pages for which there has been a great need. Through the medium of many illustrations and word description, the author has amply covered all the essential details of the correct methods of applying plaster casts.

The stress laid upon teamwork during the cast application and especially the after care with attention to the comfort of the patient is most important. Nothing can be more disturbing than an uncomfortable cast which may necessitate its

removal, reapplication, and jeopardy to the fracture reduction. When the patient complains of pain over bony prominences, the patient is always right.

A careful reading of the text by a doctor with any dexterity should result in a cast that looks trim, an indication of a well-planned appliance and an indication of careful attention to the underlying fracture. R. E. L.

Synopsis of Physiology. By ROLLAND J. MAIN. Illus. 341 pp. $3.50. *The C. V. Mosby Company, St. Louis, Missouri,* 1946.

The nine chapters of this small volume deal with protoplasm and the cell, environmental adaptation of cells and homeostasis of the body, the cardiovascular system, respiration, digestion, the nervous system, sensation, endocrines and reproduction, and the physiology of miscellaneous systems, functions and organs. The subject matter of each chapter is subdivided into numerous subtopics each of which is dealt with by means of a series of brief definite statements. As stated by the author these are frequently "shockingly dogmatic" and unsubstantiated by either evidence or references to sources of information. Although these statements are usually correct and describe the principle known facts of physiology they are not very helpful to one wishing to advance his knowledge of any one subject. Quite a few topics are treated quite satisfactorily but on the whole this book does not contain enough detailed information to meet the needs of the beginning student. Furthermore, an advanced student probably would find the book of little real use because being devoid of references it leads no where. If a student must refer eventually to a textbook from which "they recoil in horror because of its size" they might as well begin with it and avoid this additional little book. If the book serves no other purpose, it at least furnishes a little refresher course for those who have at one time obtained a rather thorough knowledge of physiology. C. McC. B.

A Textbook of Bacteriology and Immunology. By JOSEPH M. DOUGHERTY and ANTHONY J. LAMBERTI. Illus. 360 pp. $4.50. *The C. V. Mosby Company, St. Louis, Missouri,* 1946.

This is a textbook for undergraduate students, written with the purpose of presenting the fundamentals of bacteriology and immunology to pre-professional students. The style is clear and simple, the authors using only an unavoidable minimum of terms unfamiliar or confusing to the pre-medical or pre-dental student. Sufficient basic treatment is given to the various subjects to arouse and maintain the students' interest without overwhelming them with too much detailed information.

We welcome particularly the chapters on apparatus, culture media, bacteriological technique and quantitative titration. Familiarity of the graduate student with such basic subjects and their practical application would leave more time and opportunity for advanced instruction.

Presentation of the principles of immunology to beginners is an extremely difficult task. It has been solved here as efficiently as possible in a short textbook —with one exception, which is a question of organization. We feel that it would

be easier for the student to be informed first of the composition of blood, before reading the chapters on phagocytosis, complement fixation or blood groups.

The authors state in the preface that they are well aware of the criticism directed against textbooks in the college level which treat of the medical phases of bacteriology. In this book the treatment of the medical phases has been done with enough restraint, so as not to outweigh the bacteriological or laboratory side. The inclusion of the medical applications is a definite advantage of the book, as it is equally important for the student, especially the student in immunology, to realize the close interrelationship between infectious agents and their respective hosts, as it is for them to have a sound knowledge in systematic bacteriology.

We regret to have to call attention to the fact that the book contains a few misleading statements, as for instance: "penicillin is only efficient for Gram-positive organisms." Correction of such statements would greatly increase the value of the book which is otherwise well suited for the purpose for which it was written. R. H. W.

Textbook of Ophthalmology. By SANFORD R. GIFFORD. 3rd Ed. 457 pp. $4.00. *W. B. Saunders Company, Philadelphia, Pennsylvania*, 1945.

This revised edition of this standard textbook for medical students and general practitioners, prepared by Dr. Gifford before his death, is of the same high order of excellence as previous editions. Teachers of ophthalmology will be happy to know that Dr. Adler will revise future revisions of it. F. B. W.

White Versus Brown Flour. By F. L. DUNLAP. 1945.

The preface of *White Versus Brown Flour* states that it was written primarily for cereal chemists, and its interest appeal seems definitely limited to those well versed in the knowledge and terminology of the milling business. For these persons it might be a valuable compilation and survey of both domestic and foreign literature. The author quotes or refers to over three hundred articles. These quotations are used with very little connective material resulting in a lack of coherence. It is also a recognized fact that sentences or paragraphs lifted from their text lose their full meaning and one wonders if this has not been true in some instances here.

White Versus Brown Flour is purported to be an unbiased presentation of the facts about white and brown or long and short extraction flours but there is a definite feeling that it is mainly propaganda for white flour. Its sponsorship by the *Northwestern Miller*, a trade journal, and the foreword written by its managing editor does little to allay this feeling. Advocates of the use of whole wheat are dismissed for the most part as food faddists. There are many reliable nutritionists who believe that whole wheat products are a desirable adjunct to the normal person's diet. It is this group which has been largely ignored by the author. The advocates of enriched bread also ignore the fact that in the milling of white flour thirty nutrients are removed—enrichment returns only four.

The book does stimulate the reader who possesses definite opinions of the value of white flour versus brown flour to search further into the literature and to read in full some of the provocative articles quoted. V. H.

BOOKS RECEIVED FOR REVIEW

Agnosia, Apraxia, Aphasia. Their Value in Cerebral Localization. By J. M. NIELSEN. 2nd Ed. Illus. 292 pp. $5.00. *Paul B. Hoeber, Incorporated, New York, New York,* 1946.

Autopsy Diagnosis and Technic. By OTTO SAPHIR. 2nd Ed. Illus. 405 pp. $5.00. *Paul B. Hoeber, Incorporated, New York, New York,* 1946.

A Bibliography of Infantile Paralysis 1789–1944. By LUDVIG HEKTOEN AND ELLA M. SALMONSEN. 546 pp. $15.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1946.

Diagnosis and Management of the Thoracic Patient. Edited by CHARLES PHILAMORE BAILEY. 334 pp. $4.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1945.

Diseases of the Skin. By GEORGE CLINTON ANDREWS. 3rd Ed. Illus. 937 pp. $10.00. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1946.

A History of Medicine. By DOUGLAS GUTHRIE. Illus. 448 pp. $6.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1946.

Pneumoperitoneum Treatment. By ANDREW LADISLAUS BANYAI. Illus. 376 pp. $6.50. *The C. V. Mosby Company, St. Louis, Missouri,* 1946.

Principles and Practice of Tropical Medicine. By L. EVERARD NAPIER. 917 pp. $11.00. *The MacMillan Company, New York, New York.* 1946.

Public Baths and Health in England, 16th–18th Century. By CHARLES F. MULLETT. 85 pp. $1.50. *Johns Hopkins Press, Baltimore, Maryland,* 1946.

Studies on Brazilian Anophelines from the Northeast and Amazon Regions. By L. M. DEANE, O. R. CAUSEY, AND M. P. DEANE. 50 pp. $1.10. *Johns Hopkins Press, Baltimore, Maryland,* 1946.

Surgery of the Hand. By STERLING BUNNELL. Illus. 734 pp. $12.00. *J. B. Lippincott, Philadelphia, Pennsylvania,* 1944.

The Surgical Technic of Abdominal Operations. By JULIUS L. SPIVACK. 4th Ed. Illus. 712 pp. $10.00. *Charles C. Thomas, Springfield, Illinois,* 1946.

Synopsis of Pathology. By W. A. D. ANDERSON. Illus. 741 pp. $6.50. *The C. V. Mosby Company, St. Louis, Missouri,* 1946.

Textbook of Gynecology. By ARTHUR HALE CURTIS. 5th Ed. Illus. 755 pp. $8.00. *W. B. Saunders Company, Philadelphia, Pennsylvania,* 1946.

Through the Stratosphere: the Human Factor in Aviation. By MAXINE DAVIS. 253 pp. $2.75. *The MacMillan Company, New York, New York,* 1946.